REMARKS

Claims 1-7, 9-16, 18-20, 22-34 and 40-52 remain pending.

Claim Rejection: 35 U.S.C. §112, second paragraph

Claims 15 was rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claim 15 has been amended to remove the term "acellular." Claims 36 and 37 have been canceled. Reconsideration of this rejection is requested.

Claim Rejection: Rejection under 35 U.S.C. §102

Claims 1-3, 5-9, 11, 15-17, 19-25, 30-32 and 35-39 were rejected under 35 U.S.C. 102(b) as being anticipated by Vogel et. al.

Anticipation can be found only if a reference shows exactly what is claimed. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Anticipation requires identity of the claimed process and a process of the prior art; the claimed process, including each step thereof, must be described or embodied in a single reference. *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.*, 45 F.3d 1550, 22 USPQ2d 1496 (Fed. Cir. 1995).

Vogel et al. is an improper 102 reference of the claims as amended.

Vogel et al. discloses an intravenous solution of photoactivatable porphycene dyes and additional solvents and adjuvants. Col. 11., Lines 45 – 47. When the intravenous solution is be dispensed from multiple dose containers, antimicrobial agents in bacteriostatic or fungistatic concentrations must be added. Col. 12, Lines 41 – 43. Among the compounds and concentrations used as an antimicrobial agent is benzalkonium chloride (0.01%). Col. 12, Line 46. Vogel et al. discloses the use of benzalkonium chloride with the porphycene compound, but only in the context of the known use of benzalkonium chloride, that of a bactericidal agent. Benzalkonium chloride is used to prevent bacterial or fungal growth in the multiple dose container which may occur as a result of repeated extraction of porphycene compound from the multiple dose container. Vogel

does not disclose the method of use of benzalkonium chloride to disrupt the membrane of a cell thereby allowing photosensitive agents to enter the cell. That Vogel et al. uses benzalkonium chloride as an antimicrobial agent is not unexpected, as benzalkonium chloride is a well known medical disinfectant.

The anticipation rejection based on Vogel et al. is improper for the following reasons:

– Vogel does not disclose the mechanism of passing photosensitive material into the cell interior, i.e., by applying benzalkonium chloride to compromise a cell membrane so as to permit the photosensitive material to diffuse into the cell interior, and

– Vogel does not disclose a topical application, surface release, inhalation, or intravenous or subcutaneous injection of benzalkonium chloride wherein the concentration of benzalkonium chloride is within the 0.001% to 1% range at the cell site. An intravenous administration of Vogel would not result in a benzalkonium chloride concentration at a cell site within this range as the intravenously administered solution would be instantly and effectively diluted within the approximately 5 liters volume of patient's blood.

Regarding claim 1, Vogel does not disclose the step of applying a surface acting agent containing benzalkonium chloride at a concentration of between 0.001% to 1.0% to a cell membrane of a cellular organism.

Regarding claim 3, Vogel does not teach or suggest a topical application of benzalkonium chloride wherein the concentration of benzalkonium chloride is within the 0.001% to 1% range at the cell site.

Regarding claim 9, Vogel does not disclose the step of applying a surface acting agent containing benzalkonium chloride at a concentration of between 0.005% to 0.05% to a cell membrane of a cellular organism.

Regarding claim 11, Vogel does not disclose the steps of applying a surface acting agent containing benzalkonium chloride at a concentration of between 0.005% to 0.05% to a cell membrane of a cellular organism and applying light to the cellular organism for a period of between 5 sections to 1 hour.

Regarding claims 15-17 and 19-25 and 30, Vogel does not disclose the step of topically applying a surface acting agent containing benzalkonium chloride at a concentration of between 0.001% to 1.0% to a cell site with an organism.

Regarding claim 22, Vogel does not disclose the step of topically applying a surface acting agent containing benzalkonium chloride at a concentration of between 0.005% to 0.5% to a cell site with an organism.

Regarding claims 31 and 32, Vogel does not disclose the step of applying a concentration including a combination of a benzalkonium chloride compound at a concentration of between 0.001% to 1.0% and a photosensitive material to the area of cell.

Concentration of Benzalkonium Chloride

In this latest Office action, the Examiner stated:

> "Regarding the concentration of benzalkonium chloride, both applicants claims and the disclosure is [sic] originally filed are silent on the concentration of any compound or constituent thereof at the cell site, this argument is not persuasive." Paper 7, page 4.

Support for the concentration limitations of the claims is clearly found throughout the original application. For example, reference to a benzalkonium chloride concentration of between 0.001% to 1% at the cell site can be found at:

-page 19, lines 27-31 and page 20, line 1, referencing FIG. 3 (topical application at the cell site of benzalkonium chloride at concentrations ranging from 0 to 0.5%),

-page 22, lines 16 – 21 (topical application at a tissue field of a solution having benzalkonium chloride at concentrations of between 0.001% to 1%), and

-page 23, lines 1 – 10 (direct application at a biofilm cell site of a solution having benzalkonium chloride at concentrations between 0.001% to 1%).

Again, Vogel et al is silent on the concentration of benzalkonium chloride at a cell site.

Inherency

Applicant challenges the Examiner's statement:

> "Thus even assuming Vogel et al were completely ignorant of the effect of benzalkonium chloride contemplated by the applicant, thus [sic] effect, and thus the claimed disorienting, passing, and

> disruption would still inherently occur in the method of Vogel et al." paper 7, page 4.

Vogel et al does not inherently disclose the claimed disorienting, passing, and disruption at the cell site. Vogel et al discloses an IV administration of a dye solution containing trace amounts of benzalkonium chloride as an antimicrobial agent. One of ordinary skill in the art would readily appreciate that an IV solution is quickly and effectively diluted into the patient's blood volume. As a result, Vogel does not disclose the application of benzalkonium chloride at the claimed concentrations to a cell site prior to photodynamic illumination at that cell site. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a give set of circumstances is not sufficient. In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999).

In light of the amendments above, it is suggested that claims 1-3, 5-9, 11, 15-17, 19-25, 30-32, and 35-39 are not anticipated by Vogel et al. As such, we respectfully request that the rejections based thereon be withdrawn.

Claim Rejection: Rejection under 35 U.S.C. §103

Claims 1, 4, 15, 18, 31, 33-35, and 40-52 were rejected under 35 U.S.C. §103(a) as being unpatentable over Wilk '202, in combination with Wilk '675 and Vogel et al. The Examiner stated:

> "Wilk et al ('020) teach sterilizing medical equipment such as catheters using light applied internally or externally of the surface. Wilk ('675) teach the use of the irradiation and a sterilizing solution. Vogel teach a solution as claimed that can be used in conjunction with light to kill bacteria or to treat viral conditions. It would have been obvious to the artisan of ordinary skill to employ in the method of Wilk et al ('675), the solution of Vogel et al and to sterilize the long dwelling catheters etc of Wilk et al ('020), upon which biofilms form and to employ the method on other body inserted lumens such as endotracheal tubes intravenous catheters, since these are equivalent to catheters of Wilk ('020) and since these are also recognized in the art as sites which require sterilization, thus producing a method such as claimed." Paper 7, Pages 2-3.

It is submitted that this proposed combination of Wilk et al ('675), Wilk et al ('020) and Vogel is flawed as there would be no motivation to replace the IV solution of Vogel with the saline solution in Wilk ('675) or the sterilizing solution of Wilk ('020).

Wilk et al. ('020) discloses the use of a saline solution flush during a sterilization process. However, Wilk ('020) does not teach the use of a "sterilizing solution". Saline solution is not a "sterilizing solution" to one of ordinary skill in the art. The saline solution of Wilk et al. ('020) is provided to ensure electrical conductivity of the solution. As saline solution has no antimicrobial properties, such a solution is not a "sterilizing solution" as suggested by the Examiner.

Wilk et al ('675) discloses the use of a "sterilizing solution" during a sterilizing process utilizing a combination of heat and radiation. Wilk '675 does not disclose or suggest the use of photodynamic activity during a sterilization process. As a result, there is not suggestion or motivation to combine these references.

The Examiner is simply engaging in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps, an activity the Federal Circuit has repeatedly indicated as improper. *In re Gorman*, 933 F.2d 982, 19 USPQ2d 1885 (Fed. Cir. 1991). There must be some reason for the combination other than the hindsight obtained from the invention itself. *Interconnect Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 228 USPQ 90 (Fed. Cir. 1985). The Examiner has not established a prima facie case of obviousness by failing to provide the motivation or reasoning as to why the combination of references is proper.

Furthermore, as additional support to the nonobviousness of the present invention, we have submitted a product listing sheet and a published article on benzalkonium chloride. Both publications state that benzalkonium chloride is unacceptable sterilant of medical equipment. Similarly, data in FIGS. 2 and 3 suggest that benzalkonium chloride is an ineffective sterilant. It is only through the novel method employed in the present invention that benzalkonium chloride can be effectively used in a sterilization process for medical equipment. An unexpected result of the present invention is that a photodynamic therapy using benzalkonium chloride is effective

against a broad spectrum of organisms including gram positive and gram negative bacteria, funguses, viruses, spores and cancer cells.

We submit that the present invention as currently claimed is not made obvious by the combination of Wilk '020, Wilk '675 and Vogel. Consequently, we respectfully request that the rejections based thereon be withdrawn.

Claim Rejection: Rejection under 35 U.S.C. §103

Claims 1, 5, 10, 12-15, 20 and 26-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vogel et al. in combination with Nitzan et al. The Examiner stated:

> "Vogel et al teach a method of eradicating acellular or cellular organisms as claimed but does not teach adding the surface acting agent prior to the photosensitive material, or a plurality of photosensitive or surface acting agents or the light dosage rate." Paper 7, Page 3.

It is respectfully submitted that Vogel does not teach a method as claimed except for the adding the surface acting agent prior to the photosensitive material, or a plurality of photosensitive or surface acting agents or the light dose rate. Vogel does not teach or suggest the mechanism of introducing photosensitive material into a cell interior by application of benzalkonium chloride to compromise a cell membrane.

The Examiner further stated:

> "Nitzan et al teach a method of photosensitizing cells using a photosensitive surfactant mixture which will perform as claimed (The PMNP, which is made from Polymyxin B sulfate, will retain some of amount of Polymyxin B sulfate therein, and thus is considered a mixture of a plurality of surfactants) except for the specific time period between the addition of the two agents and the use of benzalkonium chloride." Paper 7, Page 3.

Nitzan et al does not disclose, teach, or suggest the method as claimed except for the specific time period between the addition of the two agents and the use of benzalkonium. Nitzan teaches the use of polycationic agent polymyxin nonapeptide (PMNP) and the photosensitizer deuteroporphyrin (DP) to eradicate the gram negative bacteria E Coli and Pseudomonas aerugenosa. Nitzan uses the PMNP to bind the PMNP-DP complex to the cell membrane, much

as a membrane specific antibody would. Neither PMNP or the PMNP-DP complex cause a disruption of the cell membrane (pp 94 1st column). Unlike the present invention, Nitzan teaches the use of a surfactant to assist in the binding of the photosensitizer to the cell membrane exterior. Nitzan does not disclose or suggest passing a photosensitizer through a surfactant-compromised cell membrane.

There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the art would make the combination to achieve the subject matter of the present claims. *See*, Symbol Technologies, Inc. v. Opticon Inc., 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991). Since no such reason, suggestion or motivation exists, the pending claims are not obvious in view of the known prior art.

Vogel discloses the use of surfactants with porphycene in the formulation of a topically applied compounds. The surfactants are used to improving the viscosity of the gel. Vogel does not disclose the use of benzalkonium chloride to improve the viscosity of a gel. It would not have been obvious to one of ordinary skill in the art to employ benzalkonium chloride in the method of Nitzan et al, since Vogel does not state that benzalkonium chloride may be added to improve gel properties.

Applicant questions the Examiner's statement that:

> "However, once the cell membrane lyses or torn open (which would clearly constitute "disorienting the cell membrane so that said cell membrane no longer functions as an effective osmotic barrier" as claimed)." Paper 7, page 5

It is unclear what this partial sentence is meant to convey. Nitzan clearly does not disclose the method of compromising the cell membrane, allowing the photosensitive material to pass into the cell interior, and then activating the photosensitive material within the cell interior to cause cell disruption. At most, Nitzan discloses a compromised cell membrane as a result of photodynamic activation of photosensitive material bound to the cell membrane exterior. Only after cell lysis is the photosensitive material of Nitzan capable of being passed through the compromised cell membrane or membrane remnants. Again, in comparison the present invention is directed to the steps of compromising a cell membrane with benzalkonium chloride, allowing

the photosensitive material to pass into the cell membrane, and then activating the photodynamic process via light activation resulting in the lysis of the cell membrane.

Nitzan teaches away from the concept of using photosensitizers and a surfactant such as benzalkonium chloride to increase the cell membrane permeability and allow the photosensitizer to enter the cell by diffusion as is disclosed in the present invention. This statement is supported by the fact that Nitzan emphasizes the importance of binding the photosensitive material to the cell membrane wall and that the nature of the totality of teaching of the reference (See In re Guley 31 USPQ 2d 1130) would direct one of ordinary skill in the art toward the use of particular surfactants which would improve the binding of photosensitive material to the cell membrane exterior, and away from the use of benzalkonium chloride to breach the cell membrane and allow the photosensitive material into the cell interior prior to photodynamic activation. Given the distinction between the functions of the surfactant of Nitzan and benzalkonium chloride of the present invention, there would be no motivation to substitute or add benzalkonium chloride with the PMNP of Nitzan. While benzalkonium chloride may "inhibit bacterial and fungal contamination of the solution" as suggested by the Examiner, that alone would not motivate one to substitute benzalkonium chloride for the solution of Nitzan as the function of the surfactant is fundamentally different between Nitzan and the present invention, i.e., to facilitate binding of photosensitive material to the cell membrane (Nitzan) and to facilitate breaching of the cell membrane so as to allow photosensitive material to accumulate within the cell interior prior to photodynamic activation (present invention). A proposed modification of Nitzan to substitute PMNP with benzalkonium chloride would not be obvious as such a modification would change the principle of operation of the prior art invention being modified. See, MPEP §2143.01, citing In re Ratti 123 USPQ 349.

As such, the claims as amended are not made obvious in light of the cited references. Consequently, we respectfully request that the rejection based on Vogel and Nitzan be withdrawn.

Demand for Documentary Proof

The Examiner continues to assert that purified PMNP will retain some amount of Polymyxin B sulfate therein. The applicant traverses such an assertion. Pursuant to M.P.E.P.

2144.02 -.03, the applicant demands that evidence supporting the Examiner's position be provided.

Nitzan et al. discloses use of a purified polymyxin nanapeptide preparation –PMNP. (p. 90). PMNP is a derivative of polymyxin B, and each compound has unique chemical structure and properties relative to the other. Polymyxin B is a relatively toxic antibiotic. PMNP is less toxic than polymyxin B and is devoid of antibiotic activity. The toxicity of polymyxin B limits its potential as a therapeutic agent. It is well known that these two different chemicals can be separated and purified via standard HPLC methods. As a result, the Examiner's assertion that purified PMNP will retain some polymyxin B is without support.

The rationale to support a rejection under 35 U.S.C. 103 should rely on logic and sound scientific principle. *In re Soli*, 317 F2d 941, 137 USPQ 797 (CCPA 1963). When the Examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided. *In re Grose*, 592 F2d 1161, 201 USPQ 57 (CCPA) 1979.

CONCLUSION

Applicant respectfully requests that the Examiner reconsider the pending claims. Please direct any questions regarding this application to John Klos at (612) 321-2806.

Respectfully submitted,
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Dated: November 7, 2003

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